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5-Aminosalicylates to maintain remission in Crohn's disease: Interpreting conflicting systematic review evidence

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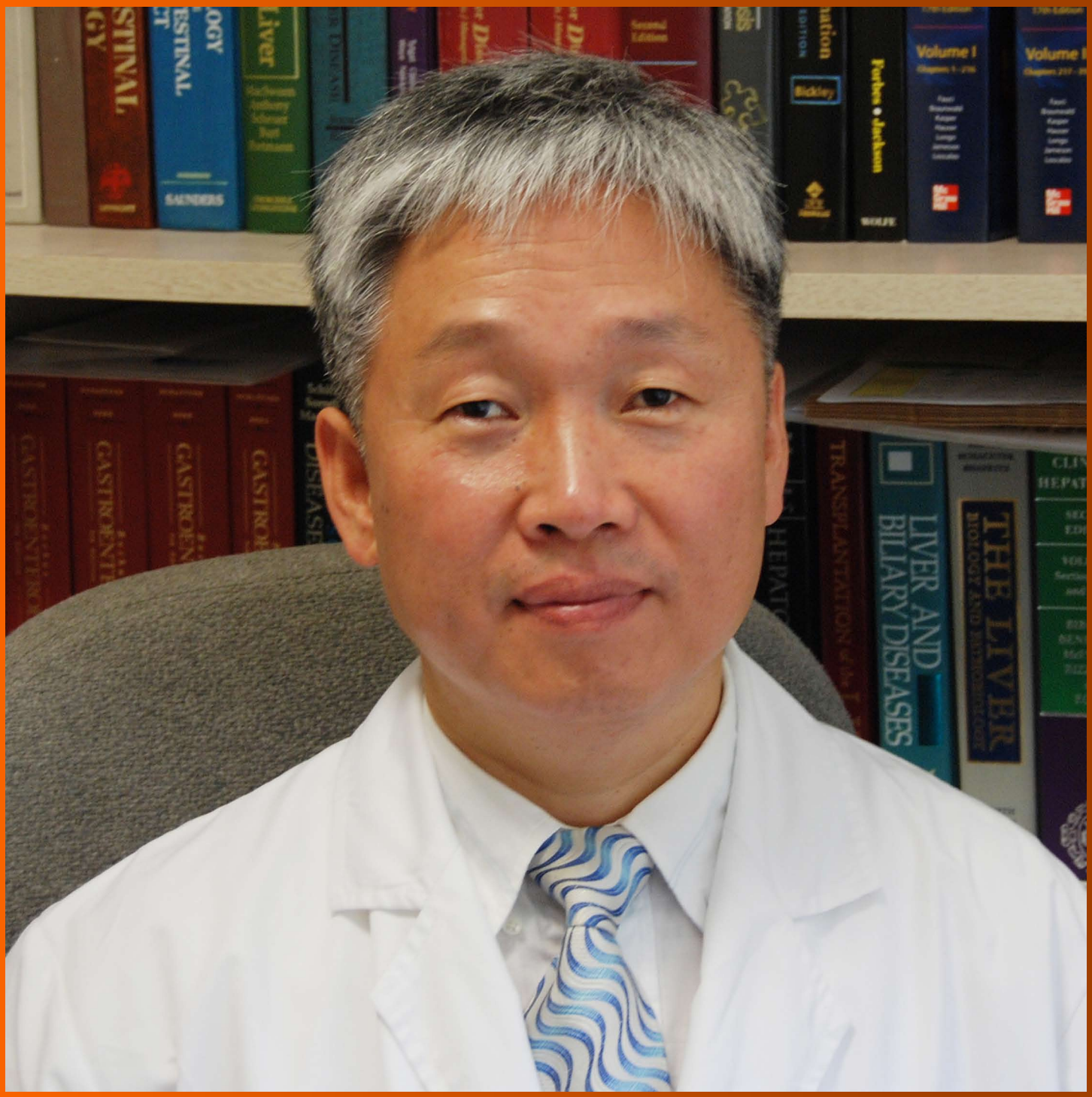

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FRONTIER

5-Aminosalicylates to maintain remission in Crohn's disease: Interpreting conflicting systematic review evidence

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Abstract

5-Aminosalicylates are a class of anti-inflammatory agents that have been used for decades in inflammatory bowel disease. Whilst they are first line for induction and an option for maintenance of remission in ulcerative colitis, the picture in Crohn's disease is variable. For maintenance of remission, key Cochrane systematic reviews have found conflicting results between the medical and surgical induced contexts. In this piece, the possible reasons for this are considered. It is proposed that clinicians should consider 5-aminosalicylates agents an option to maintain remission post-surgery. Future primary research is needed in the medical induced remission setting which considers the length of remission on enrolment and endoscopic or histological disease scores. Additionally, secondary research to rank the various treatment options in the post-surgical setting could be achieved through the use of network meta-analysis and will guide policy makers in the future.

Key words: 5-Aminosalicylate; Systematic review; Crohn's disease; Inflammatory bowel disease; Cochrane

Core tip: This paper proposes that the varying length of remission and disease activity of patients enrolled in studies for medically induced remission is different to surgical induced remission and may explain differences in findings. This guides future research proposals. Future primary research is needed in the medical induced remission setting which considers the length of remission on enrolment and endoscopic or histological disease scores. Additionally, secondary research to rank the various treatment options in the post-surgical setting could be achieved through the use of network meta-analysis.

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INTRODUCTION

There are broadly three classes of treatment that are commonly used to induce and maintain remission in inflammatory bowel disease (IBD): Antinflammatory agents, immunossupressive agents and biologic therapies. 5-aminosalicylates (5-ASAs) are a group of antiinflammatory compounds used for many years to treat IBD. The first 5-ASA used in clinical practice was to manage arthritis in the 1940s[1]. It was noted that patients who had concomitant IBD had improvements in their bowel symptoms.

COCHRANE EVIDENCE IN IBD

In the 1970s and 80s, there was growing academic and clinical concern with varying quality of primary research evidence and in particular reviews summarising evidence[2]. The concept of scientific medicine began to grow in response to this, which then became known as evidence based medicine[3]. The Cochrane Collaboration was at the forefront of evidence based medicine, leading the way in producing systematic reviews and methodological guidance for authors of reviews[4]. For 20 years, Cochrane has produced systematic reviews of primary research in human health care and health policy, and these are internationally recognized as the highest standard in evidence-based health care resources[5]. Whilst there have been criticisms of Cochrane reviews, they often inform international guidance and practice and so consideration of these reviews is vital for practising gastroenterologists.

WIDER COCHRANE EVIDENCE FOR 5-ASA AGENTS IN IBD

This class of agents have been employed in a variety of formulations within the context of IBD. In ulcerative colitis, it is well excepted in international guidance[6] and from Cochrane systematic reviews of the topic[7] that 5-ASA preparations are effective in inducing remission. Similarly, they are shown to be effective within Cochrane systematic reviews for the maintenance of remission in ulcerative colitis[8] and suggested as first line therapy for maintaining remission[6].

Interestingly despite this widespread evidence for effectiveness in ulcerative colitis, in Crohn's disease the evidence has always been more capricious. Early research demonstrated 5-ASAs are more effective for inducing remission in ileal, ileocolic, or colonic disease[9,10]. Due to this evidence, some 5-ASA agents have been frequently employed by gastroenterologists for mild Crohn's disease. However, a Cochrane review updated in 2016[11] that highlights a small benefit over placebo, but inferiority to other agents for inducing remission and mixed findings in newer studies of higher 5-ASA dosing. Until further research is performed, the authors do not suggest their use. This is also reflected in international guidance that note the variability in the evidence and do not currently suggest their use[12,13].

CONFLICTING COCHRANE EVIDENCE IN MAINTAINING REMISSION IN CROHN'S DISEASE

For maintaining remission in Crohn's disease, there is a significant difficulty in interpreting the Cochrane evidence. A recently published Cochrane review update[14] has found no evidence for the use of 5-ASA in maintaining medically induced remission. However, a review considering 5-ASA agents in post-surgical remission highlighted very different results[15]. 5-ASA was significantly more effective than placebo for averting relapses, with no statistical heterogeneity. A large number of subgroup analyses were completed to investigate length of follow up and dosage, with no change in the statistical significance of results, except when follow up was less than 12 mo. Clearly, this robust effectiveness result in the post-surgical setting[15] is at odds with the results for medically induced remission[14]. The only area of agreement between these two key reviews is related to occurrence of adverse events, with no statistical difference between 5-ASA and placebo.

The situation is further complicated in a complimentary review that investigates purine analogues for maintenance of post-surgical remission in Crohn's disease[16]. Whilst these were effective against placebo, there were only two studies in this analysis. The majority of studies compared to 5-ASA, reflecting their widespread use in this context. Meta-analysis of five studies showed no difference in preventing clinically diagnosed relapse at 12-24 mo post-surgery between 5-ASA and purine analogues. In fact, the trend in the risk ratio was towards 5-ASAs, suggesting inferiority of purine analogues. When considering adverse events that led to withdrawal of patients from treatment, these were statistically more common in the purine analogue patients compared to 5-ASA.

RECENT IMPACT ON PRACTICE GUIDANCE

As these key reviews[14-16] are reasonably contemporaneous, impact on international guidance is currently limited. However, UK guidance from the National Institute for Health and Care Excellence has recently reflected this evidence. Previous guidance clearly suggested the 5-ASA agents should not be recommended in the post-surgical settings[17], but the 2016 update now proposes 5-ASA can be offered[18] reflecting on this key Cochrane secondary evidence[15]. It remains to be seen whether other guidelines will shift advice in line with this evolving Cochrane evidence base.

UNDERSTANDING CONFLICTING RESULTS

The primary issue this spectrum of systematic review evidence raises is why 5-ASA agents have clear evidence of effectiveness in the post-surgical setting, but no

evidence in medically induced remission. There is no published research to give insight into these results, but the existing evidence base may hold the answer and allow hypotheses to be made.

Early evidence in Crohn's disease suggested that more mild disease was susceptible to 5-ASA agents[9,10], particularly in terms of the location of disease. Whilst surgery within Crohn's disease can be heterogeneous and is patient specific, it is long accepted that the most common indications relate to limited resections of particularly diseased areas with complications[19]. It is therefore possible that in the post-surgical setting, the patient has been reverted to a more disease naïve state within the remaining bowel, which due to pre-surgical medical management, is most commonly in a remission state. In many of the medical remission studies, this has been defined using clinical criteria and so at an endoscopic or histological level, there may well be disease activity. A counter view may suggest that because surgical patients had more severe disease, they do not have more mild disease. However, the author maintains that given the combination of surgical resection of these diseased areas and pre-surgical medical management, it is still likely that they represent a group with a different level of disease activity to the medical induce remission cohort of patients. This issue of clinical heterogeneity between the patient groups may explain why post-surgery evidence demonstrates efficacy of 5-ASA agents.

This hypothesis also raises a related methodological issue. Whilst studies included in the Cochrane reviews[14-16] in both medically and surgically induced remission had to define remission using accepted international rating scales, the timing of entry appears particularly capricious within the medically induced remission papers[14]. A review of the characteristics of studies suggests that patients could have been in remission for up to two years on entry within these studies. This is in stark contrast to the post-surgical remission papers reviewed that required study entry within at the most 60 d of surgery[15,16]. When this is combined with the accepted limitations of clinical disease activity scoring[20] compared to endoscopic or histological scoring methods, it is entirely possible that patients entering both sets of studies were simply not at a similar state of disease activity. In terms of 5-ASA agents and the acceptance that they are particularly efficacious in mild disease, this is a vital issue to consider.

The final issue to be considered is in the context of the post-surgical setting when comparing 5-ASA to Purine analogues. For those who have considered the individual study data within the Cochrane review[16] it will be apparent that there is clearly a contrast between primary study conclusions of purine analogue efficacy and the meta-analysis performed. This is due to the intention to treat analysis performed in the review. A per protocol analysis would suggest superiority of purine analogues, in line with the individual studies. This is not the method used in the review for several Cochrane methodological reasons related to risk of bias from incomplete outcome data. Given the clearly pervasive problem with over a quarter of patients on purine analogues not able to continue due to side effects[16] this clearly demonstrates the limitations of per protocol analysis and supports this approach from Cochrane. This was worth comment as readers may have found this discrepancy concerning. The wider relevance of this intention to treat finding is to once again suggest that 5-ASAs are not necessarily the most efficacious therapy in Crohn's disease for either induction or maintenance of remission, but there is universal agreement on their good safety profile[7,8,11,14-16].

IMPLICATIONS FOR PRACTICE

Based on the current Cochrane systematic reviews, 5-ASA agents cannot be recommended for maintenance of medically induced remission. However, in the post-surgical remission setting they are safe and effective. Given the concerning safety profile of purine analogues, it is proposed that clinicians consider this when discussing options with patients for post-surgical medication to maintain remission.

IMPLICATIONS FOR RESEARCH

There are two key areas that require further work. The first is within the medically induced remission setting. Given the volume of work suggesting the safety and potential efficacy, future large randomised controlled trials could be considered that pay particular attention to the extent and state of disease when entering the trial. Certainly, it is proposed that the use of endoscopic or histological methods to ensure induction of remission and consideration of the extent of previous disease are noted to ensure analysis can consider these factors that may be key in selecting appropriate patients for such therapy.

Secondly, given the most recent evidence now finds a role for 5-ASA agents in maintaining remission post-surgery in Crohn's disease, it is key to consider its relative efficacy to other agents, including immunosuppressive and biologic therapies. In the past, such analysis was impossible without individual primary trials investigating each comparison, but network meta-analysis offers this possibility[21]. This is a meta-analysis which allows multiple treatments to be compared directly and across trials using a common comparator, such as placebo. The end result of such analysis is to allow true conclusions to be drawn as to the relative efficacy and therefore shape future international guidance on such issues. The Cochrane Inflammatory Bowel Disease group is currently planning such a review.

CONCLUSION

It is proposed that clinicians should consider 5-ASA agents an option to maintain remission post-surgery, but evidence does not demonstrate similar efficacy in medically induced remission and so 5-ASA agents cannot be recommended in that context. Future primary research is needed in the medical induced remission setting which considers the length of remission on enrolment and endoscopic

or histological disease scores. Additionally, secondary research to rank the various treatment options in the post-surgical setting could be achieved through the use of network meta-analysis.

REFERENCES

1 **Svartz N**. Salazyoprin, a new sulfanilamide preparation: A. Therapeutic results in rheumatic polyarthritis. B. Therapeutic results in ulcerative colitis. C. Toxic manifestations in treatment with sulfanilamide preparation. *Acta Med Scand* 1942; **110**: 557-590

2 **Mulrow CD**. The medical review article: state of the science. *Ann Intern Med* 1987; **106**: 485-488 [PMID: 3813259 DOI: 10.7326/0003-4819-106-3-485]

3 **Oxman AD**, Guyatt GH. Guidelines for reading literature reviews. *Can Med Assoc J* 1988; **138**: 697-703 [PMID: 3355948]

4 **Mulrow CD**, Oxman ADeds. Cochrane Collaboration handbook. In: Cochrane Library. Issue 4. Oxford: Update Software, 1997

5 **Cochrane Collaboration**. What is Cochrane evidence and how can it help you? Available from: URL: http://www.cochrane.org/what-is-cochrane-evidence

6 **Dignass A**, Lindsay JO, Sturm A, Windsor A, Colombel JF, Allez M, D'Haens G, D'Hoore A, Mantzaris G, Novacek G, Oresland T, Reinisch W, Sans M, Stange E, Vermeire S, Travis S, Van Assche G. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 2: current management. *J Crohns Colitis* 2012; **6:** 991-1030 [PMID: 23040451 DOI: 10.1016/j.crohns.2012.09.002]

7 **Wang Y**, Parker CE, Bhanji T, Feagan BG, MacDonald JK. Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis. *Cochrane Database Syst Rev* 2016; **4**: CD000543 [PMID: 27101467 DOI: 10.1002/14651858.CD000543.pub4]

8 **Wang Y**, Parker CE, Feagan BG, MacDonald JK. Oral 5-aminosalicylic acid for maintenance of remission in ulcerative colitis. *Cochrane Database Syst Rev* 2016; **(5)**: CD000544 [PMID: 27158764 DOI: 10.1002/14651858.CD000544.pub4]

9 **Dignass A**, Van Assche G, Lindsay JO, Lémann M, Söderholm J, Colombel JF, Danese S, D'Hoore A, Gassull M, Gomollón F, Hommes DW, Michetti P, O'Morain C, Oresland T, Windsor A, Stange EF, Travis SP; European Crohn's and Colitis Organisation (ECCO). The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Current management. *J Crohns Colitis* 2010; **4**: 28-62 [DOI: 10.1016/j.crohns.2009.12.002]

10 **Travis SP**, Stange EF, Lémann M, Oresland T, Chowers Y, Forbes A, D'Haens G, Kitis G, Cortot A, Prantera C, Marteau P, Colombel JF, Gionchetti P, Bouhnik Y, Tiret E, Kroesen J, Starlinger M, Mortensen NJ. European evidence based consensus on the diagnosis and management of Crohn's disease: current management. *Gut* 2006; **55** Suppl 1: i16-i35 [PMID: 16481629 DOI: 10.1136/gut.2005.081950b]

11 **Lim WC**, Wang Y, MacDonald JK, Hanauer S. Aminosalicylates for induction of remission or response in Crohn's disease. *Cochrane Database Syst Rev* 2016; **7**: CD008870 [PMID: 27372735 DOI: 10.1002/14651858.CD008870.pub2]

12 **Gomollón F**, Dignass A, Annese V, Tilg H, Van Assche G, Lindsay JO, Peyrin-Biroulet L, Cullen GJ, Daperno M, Kucharzik T, Rieder F, Almer S, Armuzzi A, Harbord M, Langhorst J, Sans M, Chowers Y, Fiorino G, Juillerat P, Mantzaris GJ, Rizzello F, Vavricka S, Gionchetti P. 3rd European Evidence-based Consensus on the Diagnosis and Management of Crohn's Disease 2016: Part 1: Diagnosis and Medical Management. *J Crohns Colitis* 2017; **11**: 3-25 [PMID: 27660341 DOI: 10.1093/ecco-jcc/jjw168]

13 **Lichtenstein GR**, Hanauer SB, Sandborn WJ. Management of Crohn's disease in adults. *Am J Gastroenterol* 2009; **104**: 465-483; quiz 464, 484 [PMID: 19174807 DOI: 10.1038/ajg.2008.168]

14 **Akobeng AK**, Zhang D, Gordon M, MacDonald JK. Oral 5-aminosalicylic acid for maintenance of medically-induced remission in Crohn's disease. *Cochrane Database Syst Rev* 2016; **9**: CD003715 [PMID: 27681657 DOI: 10.1002/14651858.CD003715.pub3]

15 **Gordon M**, Naidoo K, Thomas AG, Akobeng AK. Oral 5-aminosalicylic acid for maintenance of surgically-induced remission in Crohn's disease. *Cochrane Database Syst Rev* 2011; Jan 19; **(1)**: CD008414 [PMID: 21249709 DOI: 10.1002/14651858.CD008414.pub2]

16 **Gordon M**, Taylor K, Akobeng AK, Thomas AG. Azathioprine and 6-mercaptopurine for maintenance of surgically-induced remission in Crohn's disease. *Cochrane Database Syst Rev* 2014; **(8)**: CD010233 [PMID: 25081347 DOI: 10.1002/14651858.CD010233.pub2]

17 **NICE guideline development group**. Crohn's disease: management in adults and children. Available from: URL: https://www.nice.org.uk/guidance/cg152/update/CG152/documents/crohns-disease-nice-version2

18 **NICE guideline development group**. Crohn's disease: management update 2016. Available from: URL: https://www.nice.org.uk/guidance/cg152/chapter/Recommendations#maintaining-remission-in-crohns-disease-after-surgery

19 **Farmer RG**, Hawk WA, Turnbull RB. Indications for surgery in Crohn's disease: analysis of 500 cases. *Gastroenterology* 1976; **71**: 245-250 [PMID: 1084841 DOI: 10.1016/S0016-5085(76)80196-5]

20 **D'Incà R**, Caccaro R. Measuring disease activity in Crohn's disease: what is currently available to the clinician. *Clin Exp Gastroenterol* 2014; **7**: 151-161 [PMID: 24876789 DOI: 10.2147/CEG.S41413]

21 **Li T**, Puhan MA, Vedula SS, Singh S, Dickersin K. Network meta-analysis-highly attractive but more methodological research is needed. *BMC Med* 2011; **9**: 79 [PMID: 21707969 DOI: 10.1186/1741-7015-9-79]

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